REMARKS

I. Status of the Claims. Upon entry of this Amendment, claims 1-22, 35, 37-39, 64 and 66-85 are pending. Claims 1-22, 35, 37, 38, 64, 66-85 have been amended.

The respective preambles of claims 1-22, 35, 64, 66-82 have been amended to recite the phrase "recombinant mutant allergen of a naturally occurring allergen." The former version of claim 1 was directed to a "recombinant allergen, characterised in that it is a mutant of a naturally occurring allergen." The amendment of the respective preambles thus does not change the scope of the claims.

Claims 1, 2, 3, 14, 15, 37, 66, 67, and 80-82 have also been amended to refer to mutations without reference to "primary" or "secondary" mutations. Support for the amendments is found, e.g., in the descriptions of "primary" and "secondary" mutations that appear in specification at page 19, line 33 through page 20, line 1 and page 24, line 27 through page 25, line 8 and in the respective original claims.

Claims 1 and 16-20 have also been amended to be directed to recombinant mutant allergens derived from naturally occurring allergens selected from the group consisting of Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens. Support for Fagales group 1 allergens is found in the specification at, e.g., page 27, line 36, page 28, lines 19-22, page 43, lines 4-9, page 44, line 29 through page 45, line 5, and original claims 20 and 21. Support for Vespidae antigen 5 allergens is found in the specification at, e.g., Fig. 10, page 28, line 16, page 28, lines 33-34 and original claims 32 and 33. Support for house dust mite group 1 allergens is found in the specification at, e.g., Fig. 35. Support for house dust mite group 2 allergens is found in the specification at, e.g., Fig. 32. Support for grass group 5 allergens is found in the specification at, e.g., Fig. 38. Support for the particular allergens set forth in claims 16-20 is found in the specification at page 28, lines 19-35.

Claims 38 and 83-86 have been amended further to replace the term "variants" with language that more clearly defines the claimed invention. The respective scopes of claims 38 and 83-86 are unchanged.

All amendments to the claims are supported by the application as filed. By this Amendment, no new matter is added to the application.

II. Examiner's Interview. On July 30, 2007, Applicants' representative Mitchell Bernstein conducted a personal interview at the USPTO with Examiners Rooney, Haddad, Szperka, Ewoldt and SPE Chan, at which time the pending rejections were discussed. Applicants' representative thanks the Examiners for the courtesies extended during the interview. No agreement on the claims was reached.

III. Response to Rejections. The rejections set forth in the Office Action are addressed as follows.

(i) Obviousness-type double patenting. Claims 1-22, 25, 26, 28, 35, 37-39, 64 and 66-85 are provisionally rejected over claims 36-96 of co-pending application no. 10/719,553 ("the '553 application"). The '553 application has not issued as a patent. Accordingly, it is requested that the instant rejection be held in abeyance.

(ii) Rejection under 35 U.S.C. §103(a). Claims 1-22, 25, 26, 28, 35, 64 and 66-82 have been rejected as obvious over and WO 99/47680 (WO '680). The Examiner's position is that WO '680 provides motivation to make a recombinant mutant Bet v 1 allergen comprising all of the mutations set forth in Ipsen and that such a mutant would read on the mutant allergens called for in the instant claims. The rejection is traversed because WO '680 provides no motivation to make the instantly claimed invention.

The Examiner errs in finding a motivation in Ipsen to make a mutant comprising all of the single mutations that are disclosed therein. The obviousness standard requires that the invention be considered as a whole and that there be a motivation to combine elements found in the prior art to arrive at the claimed invention. *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 411 F.3d 1332, 1337 (Fed. Cir. 2005). *See also KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740-1741 (2007) ("KSR") (Courts to look to prior art "in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." The mere presence of elements of the claimed invention in the prior art is not sufficient to

arrive at the claimed invention, even if it is possible to physically combine the elements. *Smiths Industries Medical Systems, Inc. v. Vital Signs, Inc.,* 183 F.3d 1347, 1356 (Fed. Cir. 1999) ("[N]o basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time of the invention.") Obviousness cannot be predicated on a combination of elements "selectively culled" from the prior art. *ATD Corp. v. Lydall, Inc.,* 159 F.3d 534, 546 (Fed. Cir. 1998). In KSR, the Supreme Court reiterated that new combinations of known elements may be patentable. *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. at 1741 . ("Patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.") The Court set forth, "It can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.*

In the instant case, there is no motivation to combine the point mutations disclosed in WO '680 to arrive at the instantly claimed recombinant allergen with at least primary mutations, spaced from each other by at least 15Å, wherein the primary mutations are placed in such a manner that at least one circular surface region with an area of 800 $Å^2$ comprises no mutation. The Examiner's asserts that there is motivation to increase the number of mutations in a mutant allergen because this will reduce IgE binding and concludes that the claimed invention is thus obvious. The Examiner, however, has failed to articulate a reason for how generally increasing the number of mutations would lead to the claimed allergens with at least primary mutations, spaced from each other by at least 15Å, wherein the primary mutations are placed in such a manner that at least one circular surface region with an area of 800 $Å^2$ comprises no mutation. *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. at 1741. Thus, the motivation asserted by the Examiner is general in nature and leads to the conclusory statement that the invention is obvious that is not the standard for obviousness. *Id.* ("Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead there must be some rational underpinning to support the legal conclusion of obviousness.") In short, these is no motivation to arrange the mutations disclosed in the absence of

a motivation to arrange the point mutants disclosed in WO '680 in the fashion called for in the instant claims. The rejection under section 103 should be withdrawn.

For at least the reasons set forth above, claims 1-22, 35, 64, and 66-82 are not obvious over the prior art of record. Reconsideration of claims 1-22, 35, 64, and 66-82 and withdrawal of the rejections under section 103 is requested.

(iii) Rejection under 35 U.S.C. §112, first paragraph (written description). Claims 1-22, 25, 26, 28, 35, 37-39, 64 and 66-82 are rejected for alleged failure to comply with the written description requirement. The Examiner's position is that the specification fails to provide adequate written description for any recombinant mutant allergen. In response, without conceding the validity of the rejection or the Examiner's position, the claims have been amended to be directed to recombinant mutant allergens of a naturally occurring allergen selected from the group consisting of Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens. *See* claim 1. The subsisting claims are thus directed to recombinant mutant allergens derived from Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens and comprising at least four mutations, which each reduce the specific IgE binding capability of the mutated allergen as compared to the IgE binding capability of the naturally occurring allergen, each of said at least four mutations being a substitution of one surface-exposed amino acid residue with another residue, which does not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic species from which said naturally occurring allergen originates, each of said at least four mutations being spaced from each other by at least 15 Å, and comprising at least one circular surface region with a area of 800 $Å^2$ that comprises no mutation.

The specification provides adequate written description for the claimed recombinant mutant allergens. The written description requirement requires that the specification provide disclosure that allows one of ordinary skill in the art of the invention to "recognize that [the inventor] invented what is claimed." *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572 (Fed. Cir. 1997); *see also Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1563-64 (Fed. Cir. 1991) (Applicant "must convey with reasonable clarity to those skilled in the art that ... he or she was in

possession *of the invention.*") (emphasis in original). The written description requirement "ensure[s] that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as detailed in the patent specification." *Reiffin v. Microsoft Corp.,* 214 F.3d 1342, 1354 (Fed. Cir. 2000). The written description requirement is met by providing sufficient structural, physical and/or functional properties that describe a genus and/or a sufficient members of genus that show the inventors were in possession of the claimed invention. *Regents of the University of California v. Eli Lilly & Co.,* 119 F.3d 1559, 1567-68 (Fed. Cir. 1997). Functional language may provide adequate written description "if in the knowledge of the art the disclosed function is sufficiently correlated with a particular, known structure." *Amgen Inc. v. Hoechst Marion Roussel, Inc.,* 314 F.3d 1313, 1332 (Fed. Cir. 2003) *citing Enzo Biochem, Inc. v. Gen-Probe, Inc.,* 296 F.3d 1316, 1324 (Fed. Cir. 2002).

The instant application sets forth the claimed invention in sufficient detail to show that Applicants were in possession of the claimed invention. Hence, the specification discloses that "the invention is based on the recognition that a mutated allergen having IgE binding reducing mutations in multiple be cell epitopes, and at least one intact epitope" would reduce crosslinking IgE, and thus the allergenicity of the mutant allergens, while preserving at least one epitope to raise an IgG response. Specification at page 18, lines 29-36. The specification discloses that the recombinant mutant allergens are produced by making substitutions of at least four surfaced-exposed, conserved amino acids that are spaced from each other by at least 15 Å, while preserving at least one circular surface region of 800 $Å^2$. Specification at, e.g., page 19, line 21-page 20, line 1. The spacing of the at least four mutations ensures that they are in separate clusters of epitopes. Specification at page 20, lines 14-17. In addition to the at least four mutations spaced at least 15 Å from each other, the recombinant mutant allergens may further comprise additional mutations ("secondary mutations") that further reduce IgE binding. Specification at page 24, line 27 through page 25, line 8. These additional mutations are also placed such that a 800 $Å^2$ area free of mutations is preserved. Specification at page 25, lines 2-3. The specification further sets forth detailed "Criteria for substitution." Specification at page 36-38.

The specification further gives detailed analysis on the structural features of Bet v 1, Der p 2, Ves v 5, Der p 1, and Phl p 5 and related proteins that further show possession of the

claimed invention. Thus, the specification discloses 57 amino acids of Bet v 1 that are highly solvent exposed and conserved (page 68), 54 amino acids of Der p 2 that are highly solvent exposed and conserved (page 72), 88 amino acids of Ves v 5 that are highly solvent exposed and conserved (page 76) and sets forth 12 Der p 2 mutants (pages 97-98), 11 Der p 1 mutants (pages 105-106), 14 Phl p 5 mutants (pages 114-115). The detailed description of amino acids to be mutated and the combinations of mutants demonstrate that the inventors had possession of the claimed invention as it relates to Bet v 1, Ves v 5, Der p 1, Der p 2, and Phl p 5. Moreover, as disclosed in the specification, Bet v 1, Ves v 5, Der p 1, Der p 2, and Phl p 5 are highly homologous to allergens Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens, respectively. See specification at page 81, lines 1-15 (67 sequences homologous to Bet v 1 within the order Fagales), page 58 and Fig. 10 A (Vespula Ag 5s about 90% identical), Fig. 35 A and B (sequence alignment of Der p 1 and other house dust mite group 1 allergens), Fig. 32 (sequence of Der p 2 with other house dust mite group 2 allergens), and Fig. 38 A-D (sequence alignment of Phl p 5 with other grass group 5 allergens). One of ordinary skill in the art would understand that the high degree of sequence identity among the members of the respective allergen families recited in the claims means that description of recombinant mutant allergens for a single member of the family provides written description for recombinant mutant allergens of any allergen within the same family. Thus, the specification provides written description for the recombinant mutant allergens called for in the subsisting claims.

In setting forth the instant rejection, the Examiner cites *Eli Lilly*, *supra*. The nature of the instant invention and the disclosure of the instant specification, however, are very different from *Eli Lilly*. In *Eli Lilly*, the Federal Circuit held that the disclosure of the sequence of a rat insulin cDNA did not provide adequate written description for the insulin cDNA sequence of every vertebrate. *Eli Lilly* at 1566-67. In *Eli Lilly*, however, the specification failed to provide any features that described the claimed vertebrate insulin cDNA. The Court found that the claimed cDNA were described solely by their function or how to obtain them. The instant case is inapposite to *Eli Lilly*. In *Eli Lilly* the claims were directed to unknown cDNA sequences. The instant claims, by contrast, are drawn to mutant allergens that are derived by making substitutions in a family of allergens, i.e., Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens, with closely related

sequences. In *Eli Lilly*, no structural features were provided that correlated with the function of the claimed vertebrate insulin cDNA. In the instant case, the specification provides that substituted amino acids are those amino acids that are conserved, solvent accessible amino acids that are spaced at least 15 Å from each other and which are each outside a circular area of 800 $Å^2$ on the surface of the allergen and goes on to list particular amino acids to choose among to make the claimed recombinant mutant allergens.

Nor does the decision of the Board of Patent Appeals and Interferences in *ex parte Kubin* (83 U.S.P.Q.2d 1410 (BPAI 2007)) support a finding that the instant specification fails to provide adequate written description for the pending claims. In *Kubin*, the Board upheld the rejection of a claim directed to isolated polynucleotides encoding polypeptides that (1) "are at least 80% identical to amino acids 22-221 of SEQ ID NO: 2" (i.e., the amino acid sequence for the extracellular domain of the protein natural killer cell activation inducing ligand ("NAIL") lacking the NAIL signal sequence) and (2) which bind to the glycoprotein CD 48. *Id.* at 1417. The specification in *Kubin* disclosed the sequence of two nucleic acids within the scope of the claim and three fusion proteins whose nucleic acid sequences would fall within the scope of the claim. *Id.* None of these sequences varied amino acids 22-221 of SEQ ID NO: 2. *Id.*

The Board in *Kubin* found that the Applicant had failed to describe what domains of within amino acids 22-221 of SEQ ID NO: 2 correlated with the function of binding CD 48, and thus the Applicant had not described which NAIL amino acids could be varied and still maintain CD 48 binding. *Id.* Citing *Eli Lilly*, the Board found that in the absence of a structure-function correlation, the claim merely defined the invention by function, which was not sufficient to satisfy the written description requirement.

Kubin is distinguished from the instant case for much the same reasons as *Eli Lilly*. In *Kubin*, the Applicant failed to provide any features of amino acids 22-221 of SEQ ID NO: 2 that correlated with binding to CD 48. As set forth above, the instant specification, in contrast, allows one of ordinary skill in the art to identify amino acids Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens. Furthermore, whereas in *Kubin* the Applicant failed to disclose any polynucleotides

encoding NAIL protein that varied in amino acids 22-221, the instant applications identifies numerous amino acid for substitution in Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens, and further sets forth examples of combinations of mutants, whereas the Applicant in *Kubin* failed to provide any working examples of polynucleotides encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO: 2 and which bind CD 48.

In short, as with *Eli Lilly*, the Applicant in *Kubin* failed to provide any structural features that correlated with the function of the polypeptide called for in the claim, whereas the instant specification sets out the features, including specific amino acids, of Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens that are called for in the claims and which allow one of ordinary skill in the mutant art to make the claimed recombinant allergens. Thus, the basis of the Board's decision in *Kubin* does not apply to the instant claims.

For at least all of the reasons set forth above, the specification provides adequate written description for the full breadth of the instantly claimed invention. Reconsideration of the claims and withdrawal of the rejection thereof for lack of written description is requested.

(iv) Rejections Under 35 U.S.C. § 112, first paragraph (enablement). Claims 1-22, 25, 26, 28, 35, 37-39, 64 and 66-82 are rejected for alleged lack of enablement. In response, the claims have been amended to be directed to recombinant mutant allergens derived from Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens.

The specification enables the full scope of the claims. At the time the application was filed three dimensional structures had been published for Bet v 1, Ves v 5, and Der p 2 Specification at page 67 lines 7-8 (3-D structure of Bet v 1 available from Protein Data Bank (PDB) -- PDB identifier 1bv1), page 67, lines 23-24 (3-D structure of Der p 2 available from Protein Data Bank (PDB) -- PDB identifier 1a9v); page 67, line 36-page 68, line 1 (3-D structure of Ves v 5 based on accession number Q05110. (N.B.: Although the specification sets forth that the coordinates are unpublished, the PDB entry states that the Ves v 5 structure was released on October

26, 2000 (attached at Tab A)). Additionally, at the time the application was filed, a robust 3-D structure of Der p 1 had been published. Topham et al., 1994, Protein Eng. 7:869-894 (Attached at Tab B). Additionally, the specification sets forth molecular structure models for Bet v 1 (Fig. 1-26 and 30), Der p 2 (Fig. 33 and 34), Der p 1 (Fig. 36 and 37), Phl p 5 (Fig. 39 and 40).

The specification further discloses 57 amino acids of Bet v 1 that are highly solvent exposed and conserved (page 68), 54 amino acids of Der p 2 that are highly solvent exposed and conserved (page 72), 88 amino acids of Ves v 5 that are highly solvent exposed and conserved (page 76) and sets forth 12 Der p 2 mutants (pages 97-98), 11 Der p 1 mutants (pages 105-106), 14 Phl p 5 mutants (pages 114-115). The specification further discloses Bet v 1, Ves v 5, Der p 1, Der p , and Phl p 5 are highly homologous to Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens, respectively. *See* specification at page 81, lines 1-15 (67 sequences homologous to Bet v 1 within the order Fagales), page 58 and Fig. 10 A (Vespula Ag 5s about 90% identical), Fig. 35 A and B (sequence alignment of Der p 1 and other house dust mite group 1 allergens), Fig. 32 (sequence of Der p 2 with other house dust group 2 mite allergens), and Fig. 38 A-D (sequence alignment of Phl p 5 with other grass group 5 allergens). Thus, at the time the application was filed, one of ordinary skill in the art could have used the structure information for Bet v 1, Ves v 5, Der p 1, Der p 2, and Phl p 5 and the homology of these allergens with other Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens, respectively, to practice the full scope of the claimed invention.

Certain issues raised by the Examiner are addressed as follows.

The Examiner states that it is not clear how one skilled in the art can determine homology because the program parameters used when making alignments influences homology calculations. In response, it is again noted that the claims have been amended to be directed to recombinant mutant allergens derived from Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens. The specification sets forth sequence alignments for Vespula Ag 5 s (Fig. 10 A), Der p 1 and other house dust mite group 1 allergens (Fig. 35 A and B), Der p 2 with other house dust mite group 2 allergens (Fig. 32) and Phl p 5 with other grass group 5 allergens (Fig. 38 A-D). Furthermore, the specification sets forth a large number of highly solvent exposed and conserved amino acids for

each of Bet v 1 (page 68), Der p 2 (page 72), and Ves v 5 (page 76). To the extent it may be necessary, one of ordinary skill in the art could set the parameters of alignment programs such that the alignments and the conserved amino acids set forth in the specification are preserved. Finally, it is noted that the large number of members and the high sequence identity among members of the respective groups of Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens would mitigate variation due to changes in parameters to sequence alignment programs used to determine homology. Accordingly, the specification enables one of ordinary skill in the to determine "homology" as used in the subsisting claims.

The Examiner indicated the claims are not enabled because they read on allergens for which no sequence or three dimensional structural data are known. In response, as set forth above in connection with the response to the written description rejection, the three dimensional structural data that has been published or which is readily obtainable the specification sets for Bet v 1, Ves v 5, Der p 1 and Der p 2 and the particular amino acids to be mutated in each of Bet v 1, Ves v 5, Der p 1, Der p 2 and Phl p 5 are set forth in the application. At the time the application was filed, the high degree of sequence identity among allergens within the Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens would have allowed one of ordinary skill in the art to make the claimed recombinant mutant allergens from any allergen that falls within the scope of the claims.

The Examiner has objected to the use of the terms "primary mutation" and "secondary mutation." In response, the claims have been amended to remove reference to "primary mutation" and "secondary mutation."

For the reasons set forth above, Applicants respectfully submit the rejection of the claims under 35 U.S.C. § 112, first paragraph for lack of enablement has been addressed and overcome. Reconsideration of the claims and withdrawal of the rejection thereof for lack of enablement under 35 U.S.C. §112, first paragraph is respectfully requested.

(v) Rejection under 35 U.S.C. §112, second paragraph). Claims 3, 15, 22, 37-39 and 83-85 have been rejected for alleged indefiniteness. The Examiner objects to the use of the terms "primary mutation" and "secondary mutation." In response, without conceding the validity of the

rejection, the claims have been amended to defined the claimed recombinant mutant allergens without use of the terms "primary mutation" or "secondary mutation."

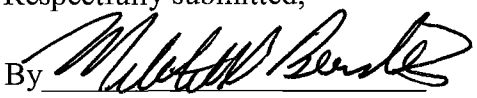
The Examiner objects to the term "variant" in claims 38 and 83-86. In response, without conceding the validity of the rejection, claims 38 and 83-86 have been amended to remove the term "variant."

The bases for all rejections under section 112, second paragraph are believed to have been addressed and overcome. Reconsideration of the claims and withdrawal of all rejections thereof for alleged indefiniteness is respectfully requested.

IV. Conclusion. This application is believed to be in condition for allowance, which is earnestly solicited. If the Examiner believes there are additional issues that may be addressed by an interview or a an Examiner's Amendment, the Examiner is invited to contact the undersigned attorney.

Dated: October 31, 2007

Respectfully submitted,

By 

Mitchell Bernstein
Registration No.: 46,550
DARBY & DARBY P.C.
P.O. Box 770
Church Street Station
New York, New York 10008-0770
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant